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Inhibitors of propagation of coagulation (factors VIII, IX and XI): a review of current therapeutic practice

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The management of patients with congenital haemophilia who develop alloantibodies against factors of the propagation phase of blood coagulation, commonly known as inhibitors, is the most important challenge facing haemophilia caregivers at present, as this complication not only compromises the efficacy of replacement therapy but also consumes an enormous amount of economic resources. Development of inhibitors further complicates the clinical course of severe haemophilia, with a prevalence of up to 30% in patients with haemophilia A (factor VIII deficiency) and up to 5% in those with haemophilia B (factor IX deficiency) and haemophilia C (factor XI deficiency). While the short-term goal of treatment of patients who develop alloantibodies is the control of bleeding, the eradication of the inhibitor is the main long-term goal. The management of severe bleeding episodes and the eradication of the autoantibody are also the mainstays of treatment of patients with acquired haemophilia, a rare but life-threatening haemorrhagic condition characterized by the development of inhibitory autoantibodies against coagulation factor VIII. The most recent options available for treating patients with congenital haemophilia complicated by inhibitors and acquired haemophilia because of autoantibodies against factor VIII are summarized in this review article.

Introduction

In patients with congenital haemophilia, the most serious and challenging complication of replacement therapy with coagulation factor concentrates is the development of alloantibodies, commonly known as inhibitors, that inhibit factors involved in the propagation phase of blood coagulation including factor VIII (FVIII, haemophilia A), factor IX (FIX, haemophilia B) or factor XI (FXI, haemophilia C) [1,2]. These inhibitory alloantibodies develop in approximately 25–30% of severe haemophilia A patients and in 3–5% of patients with haemophilia B or C. The FVIII/IX Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) defines high-responder inhibitors as those with peak activity >5 Bethesda Units (BU) and with an anamnestic rise following replacement of the deficient clotting factor [3]. Inhibitory antibodies against coagulation factors may also rarely arise as autoantibodies in non-haemophilic persons [4]. In over 98% of the cases, the inhibitor is directed against coagulation FVIII, and this leads to the acquired form of haemophilia A [4]. Inhibitors render replacement therapy ineffective, thereby precluding patients from a safe and effective standard of care and predisposing them to a high risk of morbidity and mortality [5–8].

In this review, we summarize the most important laboratory and clinical characteristics of these allo- and autoantibodies, focusing mainly on their management.

Inhibitors in congenital haemophilias

General characteristics of inhibitors of factors VIII, IX and XI

Anti-FVIII alloantibodies are polyclonal, high-affinity immunoglobulins belonging to IgG subclasses, with IgG4 over-represented. They do not bind complement and usually react with the active sites of the FVIII molecule, primarily with epitopes in the protein domains A2 (resulting in the inhibition of FVIII-FIX complex formation) and C2 (inhibition of FVIII-von Willebrand factor and FVIII-phospholipid membrane interactions), and typically display type 1 reaction kinetics [9,10]. A number of factors, both genetic (e.g. ethnicity, FVIII gene mutations, major

Table 1
Main characteristics of FVIII, FIX and FXI alloantibodies

Alloantibodies	Prevalence	Ig type	Protein domains*	Risk factors
FVIII	25–30%	IgG4	A2, C2	Genetic Genetic mutations (large deletions, nonsense mutations, *F8* gene inversions), inhibitor family history, ethnicity (African), immuno-regulatory genes (TNF-α, IL-10) Enviromental Treatment-related factors (age at first factor concentrate exposure, intensive exposure to FVIII, source of FVIII product)
FIX	3–5%	IgG4	Gla, serine protease	Genetic mutations (large deletions, stop codons, frameshift mutations)
FXI	3–5%	IgG	Various functional domains of heavy and light chains	Glu117stop mutation (Type II mutation)

TNF, tumour necrosis factor; IL, interleukin; Ig, immunoglobulin; Gla, γ-carboxyglutamic acid region. *Domains of the coagulation factor protein where epitopes of the inhibitor activity are located.

histocompatibility complex genotype, polymorphisms of immune-response genes) and environmental (e.g. number of FVIII exposure days, age at first exposure of FVIII concentrate, source of FVIII concentrate, modality and intensity of treatment) affect inhibitor formation, resulting in a complex multifactorial pathogenetic mechanism [11–16].

In haemophilia B, the prevalence of FIX inhibitors is 5–10 times lower than in haemophilia A [17]. FIX inhibitors are predominantly of the IgG4 subclass and have affinity for both the heavy and light chains of FIX. As in haemophilia A, some defects in the FIX gene (large deletions, stop codons and frameshift mutations) are associated with a greater likelihood of inhibitor development [18]. Unlike FVIII inhibitors, FIX inhibitors are accompanied in approximately half of the cases by severe anaphylactic reactions to the infusion of FIX-containing products [19, 20], which occur most often in children after relatively few exposure days (approximately 10–20) to any type of FIX-containing product [19]. FXI inhibitors are polyclonal IgG alloantibodies that act on various epitopes of the FXI molecule and inhibit activation of FXI by thrombin or FXIIa and activation of FIX by FXIa [6, 8]. Salomon *et al*. assessed the prevalence of inhibitors in 118 patients with severe FXI deficiency and found that 6% of them presented an inhibitor and that all were previously exposed to plasma replacement therapy [6]. Genotype analysis showed that all the patients with inhibitors were homozygous for the Glu117stop FXI gene mutation (so called type II mutation), which is accompanied by a baseline FXI < 1%. Thus, in patients carrying this type of mutation plasma-derived products containing FXI should be avoided as much as possible in order to prevent inhibitor formation. Table 1 summarizes the main characteristics of inhibitory alloantibodies to FVIII, FIX and FXI.

Management of factor VIII, IX and XI inhibitors

While the immediate management of inhibitors consists of treating the acute bleeding event, long-term management has the goal to eradicate the inhibitor [21].

Treatment of bleeding In haemophiliacs with low-titre inhibitors (<5 BU), acute bleeding episodes can be controlled with high doses of FVIII, FIX or FXI concentrates, which can overcome the presence of inhibitors and allow the attainment of haemostatic levels of the factor infused [22]. The recommended bolus dosage corresponds to the sum of the inhibitor neutralizing dose plus the incremental dose (i.e. the usual therapeutic dose). The neutralizing dose is obtained by multiplying the inhibitor level by the plasma volume. If needed subsequent doses correspond to the incremental dose, administered either every 6–12 h as boluses or as a continuous intravenous infusion [23].

a) Use of bypassing agents Bypassing agents, such as activated prothrombin complex concentrates (APCCs) and recombinant activated factor VII (rFVIIa, NovoSeven, Novo Nordisk A/S, Bagsværd, Denmark) are indicated for patients with high-titre inhibitors (>5 BU) that do not respond to factor infusion [22–25]. The APCC Factor Eight Inhibitor Bypassing Agent or FEIBA (Baxter, Deerfield, IL, USA) is recommended at doses of 50–100 IU kg^{-1} every 8–24 h, not exceeding 200 IU kg^{-1} per day in order to decrease the risk of thrombotic events [26]. The optimal dosage of rFVIIa ranges from 90 to 120 μg kg^{-1} [27]. The cross-over study FENOC, FEIBA Novo Seven Comparative (FENOC), comparing these two bypassing agents in the treatment of acute bleeding episodes in haemophilia A patients with inhibitors showed a high success rate with both agents (80% for FEIBA and 78% for rFVIIa) but failed to reach the goal of equivalence [28]. The results of FENOC did show substantial within-individual discordance in the efficacy of both bypassing agents, as at the 2 h time point nearly half of the patients rated one product effective and the other ineffective in terms of haemostatic efficacy [28].

A recent systematic review of studies including haemophilia A and B patients with inhibitors concluded that the overall efficacy and bleeding control rates are higher for rFVIIa than for APCC (81–91% and 64–80%, respectively) when standard dosage regimens are used to treat mild-to-

moderate bleeds in inhibitor patients [29]. Another review, which used a Bayesian meta-regression model to evaluate the outcome of more than 2000 joint bleeds, found that the cumulative rate of control of bleeding at 12, 24 and 36 h was 66%, 88% and 95% for a standard rFVIIa regimen, but was lower for standard APCC therapy (39%, 62% and 76%). These differences were statistically significant and appeared robust in sensitivity analyses [30].

On the whole, there is substantial evidence that both bypassing agents are effective in controlling acute bleeding episodes, even though the success rate is sometimes lower than that of factor concentrate in patients without inhibitors. Both products have also a good safety profile with a low thrombotic risk [31] when used according to the approved indications in patients with bleeding disorders. On the other hand, the off-label use of rFVIIa is associated with a high risk of arterial thrombosis, especially among the elderly [32]. There is no evidence that either product is more efficacious than the other, but clinicians know that some patients may respond to one product and not to the other [2]. Because recombinant FVIIa does not contain FIX, this product is also the most suitable treatment choice for haemophilia B patients with inhibitors who developed anaphylactic reactions to infused FIX [3]. Finally, rFVIIa has also been successfully used for the management of bleeding unresponsive to antifibrinolytics in FXI deficient patients with inhibitors [33].

b) High rFVIIa dosages Recently, the use of rFVIIa in bolus doses larger than the standard doses mentioned above (90 to 120 $\mu g\,kg^{-1}$) has been considered. Parameswaran *et al*. reported the results obtained in the frame of a retrospective registry of haemophilia A and B patients with inhibitors treated with various doses of rFVIIa, and reported an 84% response rate with doses $<200\ \mu g\ kg^{-1}$ and a 97% response rate with doses $>200\ \mu g\ kg^{-1}$ [34]. A prospective randomized trial compared a standard dose of rFVIIa ($90\ \mu g\ kg^{-1}$ repeated as necessary every 3 h) with a high single dose ($270\ \mu g\ kg^{-1}$) for home treatment of haemarthroses in 20 haemophiliacs with inhibitors [35]. The high-dosage rFVIIa regimen was effective, safe and required fewer rFVIIa infusions, thus simplifying home treatment. In a multicentre, randomized, double-blind, cross-over trial, Kavakli *et al*. [36] evaluated the efficacy and safety of two rFVIIa doses for treating haemarthroses in patients with congenital haemophilia A or B and inhibitors. Patients were randomly allocated to treat a first joint bleeding episode with one $270\ \mu g\ kg^{-1}$ rFVIIa dose, followed by two doses of placebo at 3 h intervals, and a second joint bleed with three single doses of $90\ \mu g\ kg^{-1}$ rFVIIa at 3 h intervals, or *vice versa*. Treatment was rated as effective for 65% of patients using the $270\ \mu g\ kg^{-1}$ dose *vs.* 70% for the $90\ \mu g\ kg^{-1} \times 3$ regimen. No safety issues were identified. Thus, the authors concluded that the administration of rFVIIa as a single $270\ \mu g\ kg^{-1}$ dose to treat haemarthroses in patients with haaemophilia and inhibitors was at least as efficacious and safe as the $90\ \mu g\ kg^{-1} \times 3$ regimen. Finally, another randomized study compared a single $270\ \mu g\ kg^{-1}$ bolus dose of rFVIIa *vs*. standard $90\ \mu g\ kg^{-1}$ doses of rFVIIa (a total of three doses were administered every 3 h) and $75\ U\ kg^{-1}$ dose of APCC (FEIBA) for the home management of joint bleeds. The authors observed a trend towards a better response with rFVIIa (successful responses were 37.5% with rFVIIa single high dose, 54.5% with rFVIIa standard dose and 27.3% with FEIBA standard dose), although differences were not statistically significant [37].

On the whole, these studies show that a single large dose of $270\ \mu g\ kg^{-1}$ rFVIIa is at least as effective as repeated smaller standard doses ($90\ \mu g\ kg^{-1}$), with obvious practical advantages in terms of conservation of the venous access particularly in children.

Prophylaxis of bleeding Bypassing agents are also increasingly being considered for secondary prophylaxis in patients with inhibitors, and early reports suggest a significant reduction of bleeding and an improvement of quality of life [38, 39]. At the moment there is only one published randomized trial of secondary prophylaxis with the rFVIIa administered with the goal to decrease the particularly high frequency of bleeding in 22 patients with haemophilia A [40]. After 3 months of secondary prophylaxis with two different daily doses of rFVIIa ($90\ \mu g\ kg^{-1}$ *vs.* $270\ \mu g\ kg^{-1}$), the patients enrolled in the study were followed for 3 additional months of on-demand treatment of bleeding episodes. There was a marked, statistically significant reduction of joint bleeding during prophylaxis, with a reduction, although non-statistically significant, of the frequency of haemarthrosis in patients randomized to the higher dose of $270\ \mu g\ kg^{-1}$ (59% reduction *vs.* 45% reduction for the $90\ \mu g\ kg^{-1}$ dosage). Surprisingly, the improvement somewhat persisted during the period of on-demand therapy, not only in terms of reduction of haemarthrosis frequency but also of more attendance at school or work [41]. A larger randomized study of secondary prophylaxis, carried out in unselected patients at an early time of inhibitor development, is currently starting (ENJOIH) [42].

On the whole, there is interest to use bypassing agents in inhibitor patients for regular prophylaxis, a method of treatment delivery that is so successful in children with uncomplicated haemophilia. Unfortunately the costs of secondary prophylaxis are huge [1], so there is a need to investigate further cost-effectiveness of this therapeutic strategy before its use can become widespread [43].

Immunoadsorption In the case of failure of bypassing agents to control bleeding, immunoadsorption may temporarily reduce the inhibitor titre in high-responder inhibitor patients, enabling effective replacement therapy with factor concentrates [44]. Freiburghaus *et al*. [45] reviewed the Malmö experience between 1980 and 1995 in 10 patients (five with haemophilia A and five with

haemophilia B) undergoing 19 procedures of immunoadsorption using staphylococcal protein A adsorption in a two-column system. In all but one case, inhibitor levels were dramatically lowered, allowing the subsequent maintenance of haemostatic levels of coagulation factors by means of factor concentrate therapy for a period long enough (usually 5 to 9 days) to stop ongoing bleeding or to prevent excessive bleeding at surgical interventions. Protein A immunoadsorption has also been successfully used in the context of immune tolerance induction (ITI) programmes (see below), in order to reduce inhibitor concentrations at the onset of treatment to levels low enough to allow delivery of a neutralizing dose of FVIII or FIX [46,47].

Other positive experiences, during or not during ITI regimens, have been recorded using immunoadsorption of anti-FVIII alloantibodies to polyclonal sheep antibodies against human immunoglobulins [48].

Inhibitor eradication by immune tolerance induction This is the only strategy able to eradicate persistent inhibitors in severe haemophilia A patients [49]. Thirty years of ITI experience have shown global success rates ranging between 60% and 80% and helped to define the patients profile associated with higher success likelihood [50]. Most data on predictors of ITI success have been identified in the frame of three large retrospective registries: the International Immune Tolerance Registry (IITR), the North American Immune Tolerance Registry (NAITR) and the German Immune Tolerance Registry (GITR) [51–53]. The FVIII dose regimens include 200–300 IU kg^{-1} day^{-1} in the GITR and 50–200 IU kg^{-1} day^{-1} in the IITR and NAITR. Low inhibitor titre before ITI start (<10 BU) and lack of high anamnestic response (historical inhibitor peak titre <200 BU) were the most consistent predictors of ITI success. In the meta-analysis of data from the IITR and NAITR, low pre-ITI inhibitor titre (<10 BU) was also associated with a more rapid tolerance [54]. However, the limits of these registries were that they retrospectively collected data differing from each other in terms of patient and treatment characteristics and particularly on the definition of end points.

In the last few years, two large-scale randomized trials, the International Immune Tolerance Induction study (I-ITI) [55] and the Rescue Immunotolerance study (RESIST) [56], have been conducted with the aim to resolve some of the unanswered questions on ITI, that is chiefly the optimal ITI regimen. However, the I-ITI study, aimed at evaluating the success rate and time to success in 150 patients with good prognostic profile (historical peak titre ≥5 BU and ≤200 BU; starting titre <10 BU) randomized to receive FVIII doses of 50 IU kg^{-1} three times weekly or 200 IU kg^{-1} daily, was interrupted prematurely because of safety concerns. A significantly greater cumulative number of bleeding episodes in joint and non-joint sites was indeed observed in the low-dose arm *vs*. the high-dose arm, at all stages of ITI, but particularly in the first ITI phase, when inhibitors were still detectable [57]. At study termination, although no sufficient power proving therapeutic equivalence was reached, ITI success rates were not different in the two treatment arms. However, median time to achieve negative inhibitor titre and normal FVIII recovery were significantly shorter (about 50%) in patients receiving the high-dose regimen. Thus, the earlier attainment of tolerance with the higher dosage (and hence of measurable FVIII levels in plasma) perhaps explains the difference in the number of bleeding episodes between the two arms.

There are fewer published reports of ITI in haemophilia B, given the fact that FIX inhibitors are rarer. At variance with results in patients with FVIII inhibitors, the success of ITI in eradicating FIX inhibitors is low, particularly in patients who develop anaphylactic reactions [25]. Among 16 haemophilia B patients in the NAITR who completed ITI, five had a successful outcome using FIX dosing regimens that ranged from 43 to 200 IU kg^{-1} day^{-1} [53]. Adverse events were reported during 11 of 17 (65%) ITI courses, a frequency 10 times higher than that for persons with FVIII inhibitors. Anaphylactic reactions accounted for 11 of the 14 adverse events and represented the major reason for failure in at least four of 11 unsuccessful courses of ITI in haemophilia B. Moreover, an association between those reactions to FIX in patients undergoing ITI and the development of the nephrotic syndrome was observed, because three of the 10 patients with those reactions developed this renal complication. The ISTH Registry on FIX inhibitors data showed that ITI was successful in only five of the 34 patients (15%) in whom it was attempted, and two of these patients had low-responder inhibitors [8]. Moreover, 13 of the 34 patients (38%) developed the nephrotic syndrome during ITI.

With the aim to provide useful information to haemophilia caregivers, an international panel of experts developed consensus recommendations for ITI, with ratings based on the level of supporting evidence [49]. For haemophilia A, the initiation of ITI was recommended after the inhibitor titre dropped to <10 BU (level IIb). While among good-risk patients (i.e. historical peak titre <200 BU, pre-ITI titre <10 BU, <5 years since diagnosis) no dosing regimen is clearly superior to another, among poor-risk patients (i.e. historical peak titre >200 BU, pre-ITI titre >10 BU, >5 years since diagnosis) a higher success rate was obtained with the use of high-dose regimens (≥200 IU kg^{-1} day^{-1}; level IIb). The consensus recommendations on the FVIII product type were that ITI is successful using FVIII products regardless of VWF content, with no definitive evidence supporting the superiority of any FVIII product, and that most patients can be effectively tolerized with the same FVIII product in use at the time of inhibitor detection (level IIb).

For haemophilia B, the panel concluded that evidence was insufficient to recommend ITI or to establish predictors for success or failure to ITI. If a decision to start ITI is made, the inclusion of a routine urinalysis is recommended in the follow-up in order to detect proteinuria and early nephrotic syndrome (level IV). As for FIX inhibitors, there are no solid data on the responsiveness to ITI in patients

Table 2

Therapeutic options for haemophilia patients with FVIII, FIX and FXI alloantibodies

Treatment of bleeding	
Low-titre inhibitors (<5 BU)	High doses of factor concentrates
High-titre inhibitors (>5 BU)	
First line	rFVIIa, APCC
Second line	Immunoadsorption
Inhibitor eradication	
First line	Immune tolerance induction*
Second line	Rituximab

rFVIIa, recombinant activated factor VII; APCC, activated prothrombin complex concentrates. *The immune tolerance induction success in eradicating FIX and FXI alloantibodies is low.

Table 3

Therepeutic options for acquired haemophilia A

Antihaemorrhagic treatment	
First line	rFVIIa, APCC
Alternative treatment*	FVIII concentrates, DDAVP
Second line	Immunoadsorption or plasmapheresis
Inhibitor eradication	
First line	Corticosteroids ± cyclophosphamide
Second line	Rituximab ± corticosteroids
Alternative treatment	Azathioprine, vincristine, mycophenolate, ciclosporin, intravenous immunoglobulin

rFVIIa, recombinant activated factor VII; APCC, activated prothrombin complex concentrates; DDAVP, desmopressin. *Low-titre inhibitors and minor bleeding.

with a persistent FXI inhibitor [58]. Table 2 summarizes the therapeutic options for the management of FVIII, FIX and FXI alloantibodies.

Finally, it is important to mention that some recent data suggest that the addition of rituximab (a monoclonal antibody against CD20-positive B cells) may improve response rates in patients with incomplete or no response to the ITI regimen. However, published experience with this agent in the treatment of alloantibodies associated with congenital haemophilia is limited to case reports or small case series [59].

Acquired haemophilia

General characteristics of acquired factor VIII inhibitors

Acquired inhibitors against FVIII occur rarely in the non-haemophilic population, with an incidence of between 1.3 and 1.5 cases per million annually [60–62]. Although uncommon, these autoantibodies are associated with a high rate of morbidity and mortality, because severe bleeds occur in up to 90% of affected patients and the mortality rate is high, ranging from 8% to 22% [63, 64]. The age distribution of autoantibodies is typically biphasic with a small peak between 20 and 30 years, because of post-partum inhibitors, and a major peak in elderly patients. The incidence in men and women is similar, except in the age ranges 20–40 years when the effect of pregnancy leads to a higher prevalence in women. In approximately 50% of cases, factor VIII autoantibodies occur in patients with no concomitant disease, while the remaining cases may be associated with the post-partum period, autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, thyroid disorders), haematological or solid cancers, infections or use of medications [65–68].

The bleeding pattern of acquired haemophilia is rather different from that of congenital haemophilia A. Most patients with FVIII autoantibodies have haemorrhages into the skin, muscles or soft tissues and mucous membranes (e.g. epistaxis, gastrointestinal and urological bleeds, retroperitoneal haematomas, post-partum bleeding), whereas haemarthroses, a typical feature of congenital FVIII deficiency, are uncommon [62]. The haemorrhages are often serious and the disease may manifest more dramatically by life-threatening bleeding following trauma or surgery or by cerebral haemorrhage.

Factor VIII autoantibodies are mostly IgG1 and IgG4 autoantibodies, often acting with second-order kinetics and reacting with the same regions of the FVIII molecule targeted by alloantibodies (i.e. A2 and C2 domains). The diagnosis of acquired haemophilia in a patient with no previous personal or family history of bleeding is typically based upon the initial detection of an isolated prolongation of the activated partial thromboplastin time (APTT), which cannot be corrected by incubating for 2 h at 37°C equal volumes of patient and normal plasma, and subsequent identification of a low FVIII level with evidence of FVIII inhibitory activity (titrated using the Bethesda method) [4, 69].

Management of acquired factor VIII inhibitors

Similar to the treatment of FVIII alloantibodies, the management of acquired haemophilia A is directed to the control of bleeding episodes and the eradication of the inhibitor [70] (Table 3).

Treatment of bleeding Efficient haemostasis can be achieved with a variety of methods that, if necessary, may be used in combination: normalization/correction of FVIII deficiency (human plasma derived or recombinant FVIII concentrates, desmopressin), bypassing the inhibitor activity (FEIBA or rFVIIa), neutralization of the inhibitor by idiotypic anti-FVIII antibodies (high-dose immunoglobulin) and removal of the inhibitor by plasmapheresis or immunoadsorption. The choice of the most appropriate therapeutic strategy depends on the site and severity of the haemorrhage, patient characteristics, underlying disorder and

inhibitor titre [71, 72]. FVIII replacement therapy is the treatment of choice when bleeding is minor and the inhibitor titre low (<5 BU). A loading dose is given as bolus to neutralize the inhibitor and to achieve haemostatic FVIII levels, followed by maintenance doses given by bolus or continuous infusion. The experience with desmopressin in acquired haemophilia is very limited and available data indicate that it may be useful only in patients with a low-titre inhibitor for the treatment of minor bleeding episodes [73].

Bypassing agents are recommended as first-line treatment for severe bleeds and both rFVIIa and FEIBA are effective, although there are no comparative trials to demonstrate superior efficacy for either product [74]. Sallah retrospectively analysed the efficacy of FEIBA in 34 acquired haemophilia patients and reported 100% haemostatic efficacy for moderate bleeds and 75% for severe bleeds, with an overall response rate of 86% [75]. In a retrospective analysis of 38 patients, Hay *et al*. [76] reported a positive response in 100% of patients when rFVIIa was used as a first-line treatment, and a positive response in 75% of patients when it was used as salvage therapy after failure of therapy with blood products.

Recently, Sumner *et al*. [77] collected the available data on the compassionate use of rFVIIa in acquired haemophilia patients from the Haemophilia and Thrombosis Research Society (HTRS) registry and the published literature. A total of 139 patients were treated with rFVIIa for 204 bleeding episodes. The overall success rate (complete or partial) of rFVIIa was 88% (161/182 bleeding episodes evaluable). rFVIIa as a first-line treatment was effective overall in 95% of bleeding episodes compared with 80% when it was used as salvage therapy after failure of other haemostatic agents.

High-dose immunoglobulins have also been used in acquired haemophilia. In a prospective multicentre study, 19 patients with low-titre inhibitors were treated with 400 mg kg^{-1} for 5 consecutive days or 1000 mg kg^{-1} for 2 days, with an overall response rate of 25% [78]. Thus, high-dose immunoglobulins are not the first choice for the eradication of FVIII autoantibodies, but may play a role as adjunctive therapy to other inhibitor eradicating treatments (steroids, immunoadsorption, immune tolerance regimens) [70]. In patients with a high-titre inhibitor and severe haemorrhages, the extracorporeal removal of the autoantibody by therapeutic plasmapheresis or its immunoadsorption to staphylococcal protein A or to polyclonal sheep antibodies against human immunoglobulins can be used prior to factor concentrate treatment [44].

Inhibitor eradication In acquired haemophilia, inhibitor eradication may be obtained with immunosuppressive agents including corticosteroids and drugs such as cyclophosphamide, azathioprine, 6-mercaptopurine and vincristine [79–83]. In their meta-analysis combining data from 20 reports, Delgado *et al*. [61] concluded that cyclophosphamide was superior to prednisone in terms of inhibitor eradication, but not in terms of overall survival. The combined data from uncontrolled cohort studies recently reviewed by Collins [72] suggested a benefit for combined steroids and cytotoxic agents. More recently, biotherapy with rituximab has also been used to treat patients with acquired haemophilia, with high success rates [84, 85]. A literature review collecting 65 patients with acquired haemophilia A treated with rituximab found that a complete or partial response was reached in more than 90% of cases [86]. Finally, preliminary data from ongoing studies have supported the effectiveness of ITI protocols in eradicating inhibitors also in patients with acquired haemophilia [87, 88].

Conclusions

In the last two decades, remarkable progress has been made in the management of patients with inhibitors of coagulation factors of the propagation phase of blood coagulation. In particular, the introduction of bypassing agents has dramatically improved the management of acute bleeding, allowing home treatment with a substantial amelioration of patient quality of life. At the same time, the widespread implementation of ITI has permitted inhibitor eradication in an increasing number of patients, so that the life expectancy in inhibitor patients has become similar to that of severe haemophiliacs without inhibitors [89, 90]. Pertaining to innovative therapies, rituximab has been shown to be a promising agent for ITI-resistant patients, which warrants further investigation in large prospective studies. This agent is indeed a strong candidate therapy for the eradication of autoantibodies in acquired haemophilia.

Finally, efforts are currently being made to reveal more about the pathophysiology of the development of inhibitors and of possible therapeutic strategies. For instance, an ongoing randomized trial (SIPPET study) is tackling the issue of whether or not there is a difference in inhibitor formation in congenital haemophilia between children previously untreated or minimally treated with plasma-derived, VWF-containing FVIII products, compared with children treated exclusively with recombinant FVIII [91, 92]. Ultimately, future insights into the understanding of the immunobiology of inhibitor formation will unlock the key to the design of more tailored and cost-effective therapies for the management and prevention of inhibitors.

Competing Interests

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